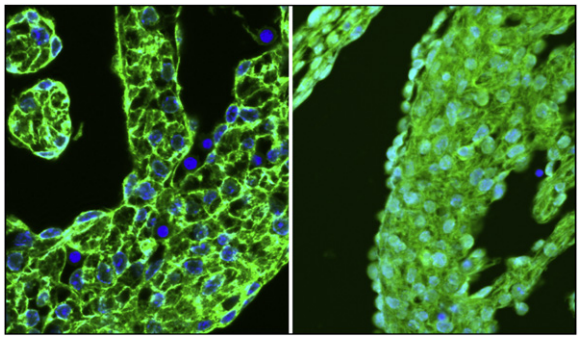
Cardiac Damage and Its Repair

Cardiomyocytes are the body's ultimate endurance specialists. Recent advances provide insight into how cardiomyocytes respond to injury and stress and reveal pathways that control cardiac growth in development and disease. These findings point to new potential therapies for heart disease, including a surprising intervention that wakes up dormant cardiomyocyte precursors after ischemic injury.



The amount of nuclear-localized β -catenin (green) is greater in *Hippo*-mutant cardiomyocytes (right) than in control cells (left). Image courtesy of T. Heallen.

Hippo Squashes Wnt Targets

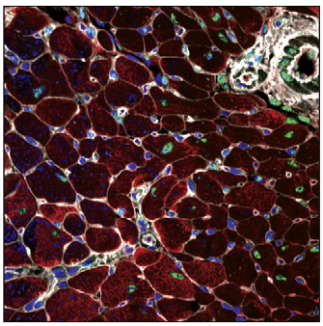
In *Drosophila*, the Hippo-signaling pathway is a well-known orchestrator of organismal size. Probing whether these mechanisms also mould organogenesis in mammals, James Martin and colleagues disrupted multiple Hippo pathway components in the developing mouse heart. These targets for conditional knockout include the MST kinases (the mammalian Hippo homologues), Salvador (a scaffold protein that binds to MST kinases), and the kinase LATS2 (a substrate of MST1/2). They show that disruption of this pathway stimulates overgrowth of the heart due to an increase in cardiomyocyte proliferation, which leads to additional malformations, including defects in the ventricular septum. Further analysis showed that Wnt target genes are upregulated upon loss of the Hippo pathway and that reducing levels of β-catenin (a core mediator of Wnt signaling) suppressed cardiac overgrowth. Moreover, the authors report a new element in the crosstalk between the Hippo and Wnt pathways. When Hippo is inactive, the LATS2 substrate YAP is not phosphorylated and accumulates in the nucleus, where it directly interacts with β-catenin. The resulting complex is recruited to growth-promoting genes, including *Sox2* and *Snai2*, activating their transcription. Future work may determine whether diminished signaling via this pathway might contribute to the pathological reactivation of developmental programs in cardiac hypertrophy.

Heallen, T., et al. (2011). Science 332, 458–461.

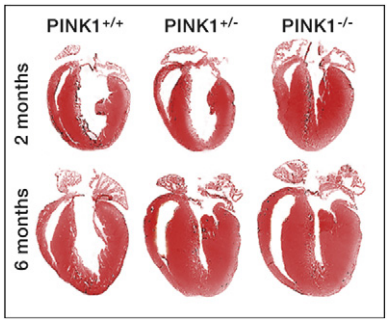
Under Pressure, TGF-β Becomes a Collaborator

Hypertension places heightened strain on the heart, which can ultimately lead to pathological changes such as hypertrophy and fibrosis. According to new work by David Kass and colleagues, one factor contributing to these maladaptive responses is elevated signaling by transforming growth factor β (TGFβ). After inducing pressure overload in the mouse heart using transverse aortic constriction, the authors observe a gradual increase in TGFβ signaling over the course of 9 weeks, which coincides with a progressive worsening of cardiac hypertrophy and dysfunction. Remarkably, the pathological changes that occur are suppressed by the cardiomyocyte-specific knockdown of the TGFβ type 2 receptor (but interestingly, not type 1 nor treatment with a neutralizing antibody directed at TGFβ). At the organ level, loss of the receptor preserved the density of capillaries in the myocardium, consistent with the notion that maintenance or growth of the vasculature during hypertrophy could be protective against the transition to heart failure. Delving further into the molecular mechanisms of this effect, the authors provide evidence that the noncanonical arm of the TGFβ pathway (which is not dependent on SMAD proteins) is of particular importance, specifically the regulation the kinase TAK1 and downstream expression of bone morphogentic protein 7 (BMP7). Whether TAK1 or BMP7 might be targets for intervention awaits exploration in future work.

Koitabashi, N., et al. (2011). J. Clin. Invest. 121, 2301–2312.



Phosphorylated SMAD (green) in myocytes, fibroblasts, and smooth muscle cells. Image courtesy of D. Kass.



Masson stain of myocardial longitudinal sections. Image courtesy of T. Mak.

Cardiomyocytes Defended by a ROS Responder

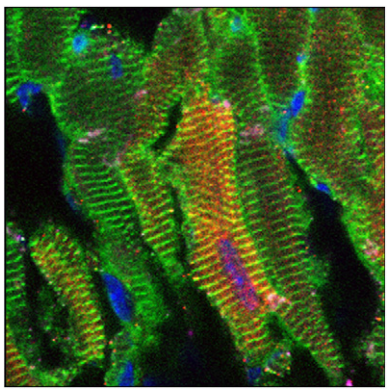
Oxidative stress contributes to cardiac hypertrophy, and thus understanding how the heart copes with its effects could lead to new therapeutic approaches for heart disease. In a recent report, Tak Mak and colleagues implicate the mitochondrial protein PTEN inducible kinase 1 (PINK1) in the protection of cardiomyocytes against reactive oxygen species (ROS). In a mouse model, the authors show that PINK1 deficiency promotes cardiac hypertrophy, increases the level of ROS, and enhances the susceptibility of cardiomyocytes to ROS-induced cell death. At the cellular level, PINK1 deficiency is shown to diminish the mitochondrial membrane potential in a ROS-dependent manner. These phenotypes are not rescued by a kinase dead version of PINK1, suggesting that identifying its relevant substrates in the heart will provide further insight into disease mechanisms. The study also provides a connection to human disease, reporting that expression of PINK1 is decreased in patients with end-stage heart failure. Although PINK1 is best known for its role in neuroprotection given that recessive mutations in PINK1 cause early-onset Parkinson's disease, this study raises the question of whether human PINK1 mutations or polymorphisms might also contribute to cardiac phenotypes.

Billia, F., et al. (2011). Proc. Natl. Acad. Sci. USA 108, 9572–9577.

Endogenous Progenitors Nearing Prime Time

Prior work has reported that cardiomyocytes can arise from progenitor cells in the outer layer of the heart known as the epicardium. Paul Riley and coworkers now describe a means of reawakening this population of cells in adulthood in order to promote the repair of damage caused by ischemic injury. Their approach involves ''priming'' this population of cells via the intraperitoneal injection of thymosin β4 prior to the induction of a myocardial infarct. This treatment reactivates expression of Wilm's tumor 1 (Wt1), a marker of the epicardium in embryonic development that is lost later in life. The cells that are induced can differentiate into cardiomyocytes and thus serve as an endogenous source for repair. The authors had previously demonstrated that this technique induces progenitors with the capacity to form new coronary blood vessels. Thus, the current findings suggest that thymosin β4 may elicit a broad spectrum of effects to reestablish an embryonic-like state in the adult heart. Ascertaining how the effects of thymosin β4 are mediated may reveal additional therapeutic targets to pursue or could provide clues for unlocking the regenerative potential of other tissues damaged by injury or affected by age.

Smart, N., et al. (2011). Nature. Published online June 8, 2011. 10.1038/nature10188.



A progenitor-derived cardiomyocyte (red) bordering on a region of injured myocardium (black areas). Image courtesy of P. Riley.

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